II. REMARKS

Formal Matters

Claims 1-10, and 16-30 are pending after entry of the amendments set forth herein.

Claims 1-5, 8, 9, and 16-19 were examined and were rejected. Claims 6, 7, 10, and 20-25 were withdrawn from consideration.

Claim 3 is amended. The amendments to claim 3 were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. Support for the amendments to claim 3 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: paragraphs 0042 and 0058. Accordingly, no new matter is added by these amendments.

Claims 26-30 are added. Support for new claims 26-30 is found in the claims as originally filed, and throughout the specification, including the following exemplary locations: claims 26-29: paragraph 0071; and claim 30: paragraph 0079. Accordingly, no new matter is added by these new claims.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Rejection under 35 U.S.C. §112, first paragraph

Claims 3-5, 8, 9, and 16-19 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

The Office Action stated that it would require undue experimentation for one skilled in the art to determine what hGH-based prolactin receptor antagonist in combination with zinc would function to predictably prevent a prolactin receptor-related condition in a subject.

Without conceding as to the correctness of this rejection, claim 3 is amended to recite "reducing the risk that an individual will acquire" a prolactin receptor-related condition.

Conclusion as to the rejection under 35 U.S.C. §112, first paragraph

Applicants submit that the rejection of claims 3-5, 8, 9, and 16-19 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejections under 35 U.S.C. §103(a)

Claims 1-5, 8, 9, 16, and 18 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 6,429,186 ('186) in view of Fuh and Wells ((1995) *J. Biol. Chem.* 270:13133; "Fuh"). Claim 17 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the '186 patent in view of Fuh, and further in view of Aamodt et al. ((1979) *Am. J. Clin. Nutr.* 32:559; "Aamodt"). Claim 19 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the '186 patent in view of Fuh, and further in view of Chen et al. ((1999) *Clin. Cancer Res.* 5:3583; "Chen").

Claims 1-5, 8, 9, 16, and 18 over the '186 patent in view of Fuh

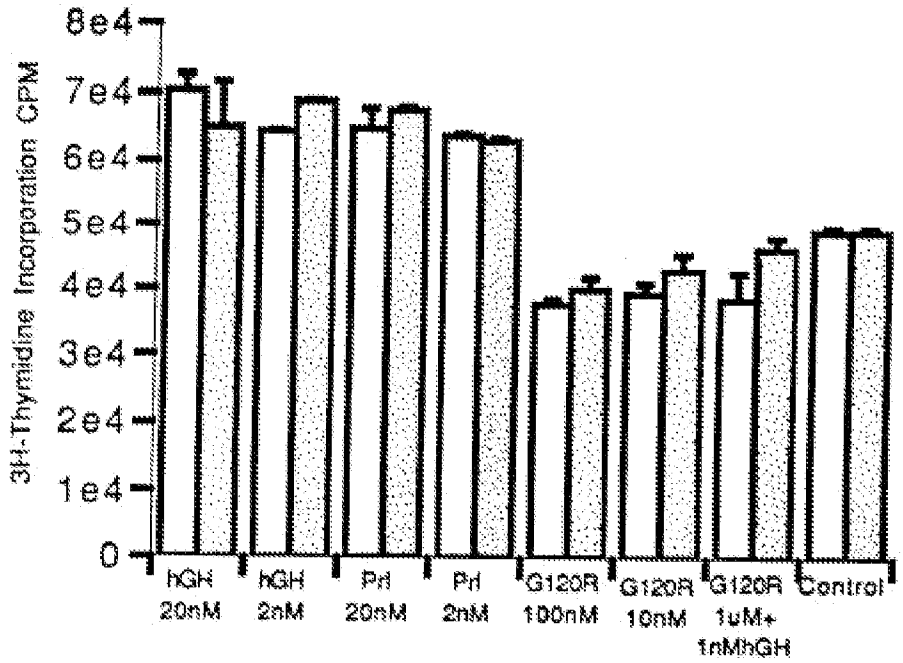
The Office Action stated that:

1) the '186 patent teaches a method of treating breast cancer in a patient comprising administering human growth hormone (hGH) mutant G120R;
2) the '186 patent demonstrates that the addition of zinc, $ZnSO_4$, increased the antagonistic effect of G120R on breast cancer cell growth, teaches zinc is required for binding of hGH to the prolactin receptor, and teaches that zinc increases the affinity of hGH to the prolactin receptor;
3) the '186 patent does not teach administering zinc to the breast cancer patient in addition to the G120R hGH mutant;
4) Fuh demonstrates that hGH mutant G120R inhibited the growth of breast cancer cells, and the addition of zinc, $ZnSO_4$, increased the antagonistic effect of G120R on breast cancer cell growth.

The Office Action concluded that one would have been motivated to administer zinc in combination with hGH mutant G120R to breast tissue for the treatment of breast cancer "because G120R inhibits the growth of breast cancer cells and zinc is required for binding of G120R to prolactin receptors in breast cancer." Office Action, page 7. Applicants respectfully traverse the rejection.

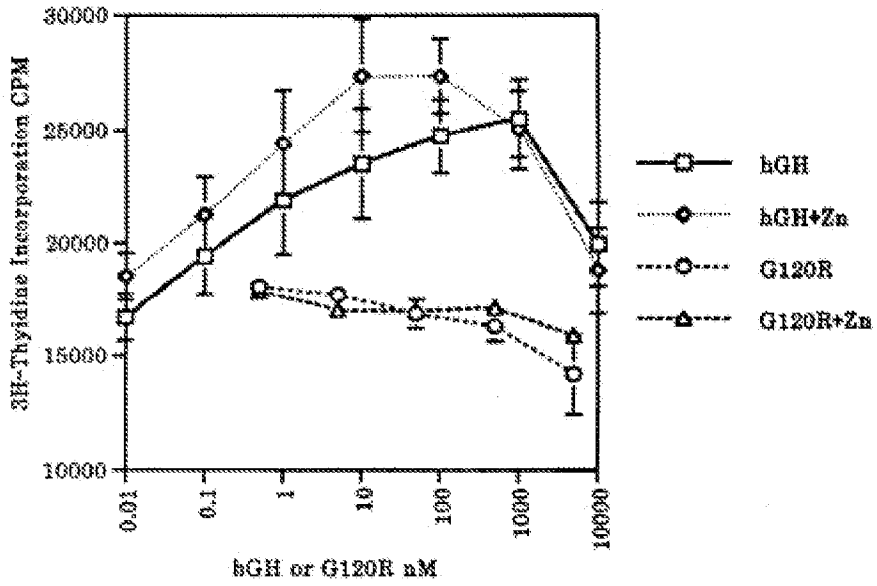
The data presented in the '186 patent does not show any significant difference in growth of breast cancer cell lines when exposed to the hGH G120R mutant versus the hGH G120R mutant plus $ZnSO_4$. When one looks carefully at the data shown in Figures 16, 17a, and 17b, it is apparent that $ZnSO_4$ had no significant effect on the growth of the breast cancer cell line T47D exposed to the hGH G120R mutant (G120R-hGH).

Figure 16 of the '186 patent is reproduced below:



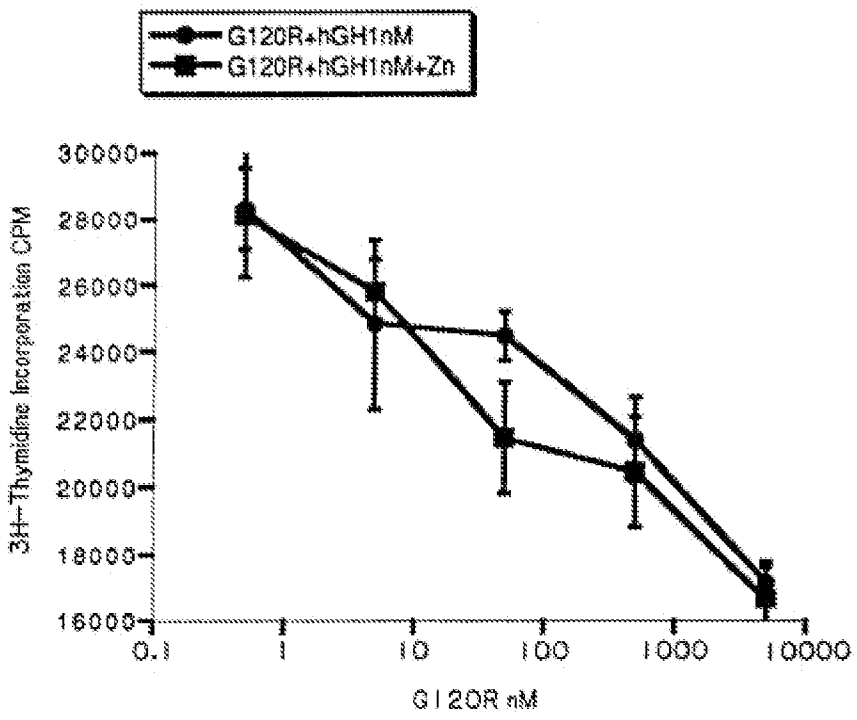
As stated at column 7, lines 10-16, of the '186 patent, Figure 16 shows the T47D (a breast cancer cell line) response to hGH or G120R-hGH, where gray bars represent assays with 26 μM $ZnSO_4$. As can be seen in Figure 16, growth of T47D cells in the presence of $ZnSO_4$ and G120R-hGH was actually slightly higher than growth of T47D cells in the presence of G120R-hGH alone. Indeed, the '186 patent states that "Addition of zinc **did not make any obvious differences**." '186 patent, column 42, lines 13-21; emphasis added.

Figure 17a of the '186 patent is reproduced below:



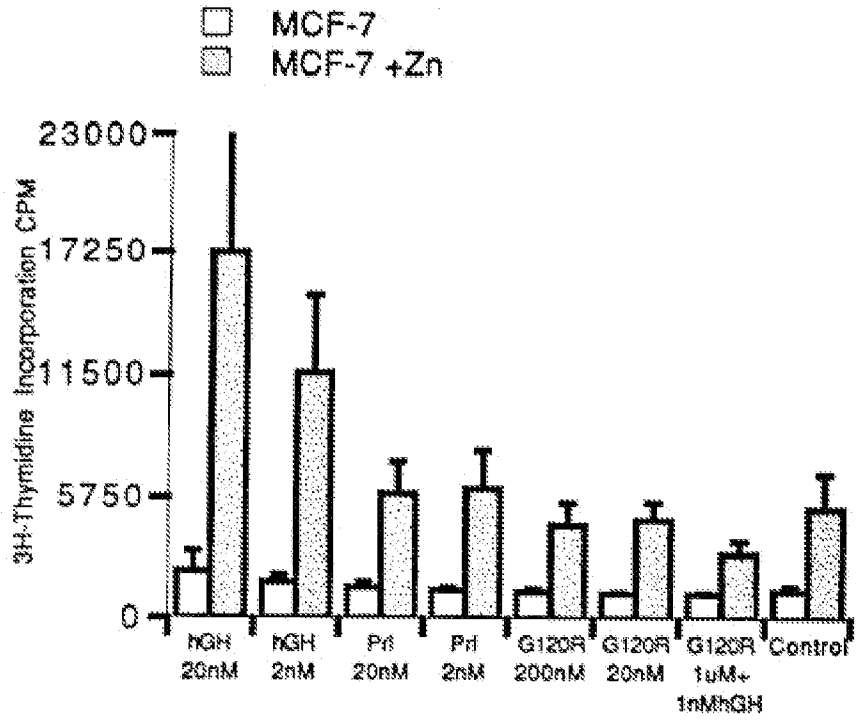
As stated at column 7, lines 17-24 of the '186 patent, Figure 17a shows the results of a dose-response assay of hGH or G120R-hGH on T47D cell proliferation, with or without 25 μM $ZnSO_4$. As is apparent from Figure 17a, the addition of $ZnSO_4$ had no significant effect on the growth-inhibiting effect of G120R-hGH.

Figure 17b of the '186 patent is reproduced below:



The Office Action asserted that Figure 17b "demonstrates that the addition of zinc, $ZnSO_4$ increased the antagonistic effect of G120R-hGH on breast cancer cell growth." Office Action, page 6. However, Figure 17b demonstrates no such thing. Indeed, in the discussion of Figure 17b in the '186, there is no mention of any effect at all of $ZnSO_4$ on G120R-hGH-mediated growth inhibition.

It is further noted that Figure 18 of the '186 patent, which shows the effect of hGH or G120R-hGH on growth of MCF-7 (a breast cancer cell line), also shows no increase in G120R--hGH-mediated growth inhibition in the presence of $ZnSO_4$. Figure 18 is reproduced below:



The Office Action noted that the '186 states that zinc is required for the binding of hGH (see column 42, lines 34-35 of the '186 patent). However, hGH is an agonist, not an antagonist, of the prolactin receptor. The '186 patent does not disclose or suggest that zinc would increase a growth-inhibitory effect of an antagonist. Indeed, as discussed above, and as the '186 patent itself states, the data presented in the '186 patent indicate that $ZnSO_4$ had no significant effect on the growth-inhibitory effect of G120R-hGH. '186 patent, Figures 16, 17a, 17b, and 18; and column 42, lines 15-18.

Because the data presented in the '186 patent indicate that $ZnSO_4$ had no significant effect on the growth-inhibitory effect of G120R-hGH, the '186 patent **does not provide a reasonable expectation of success**, and

indeed actually **teaches away** from a method as recited in instant claims 1-3 (and claims depending directly or indirectly therefrom) involving administering a hGH-based prolactin receptor antagonist and zinc.

Fuh does not cure the deficiencies of the '186 patent. Fuh presents a study of the effect of hGH, human prolactin (hPRL), and G120R variants of hGH and hPRL, on the proliferation of three different breast cancer cell lines: T47D, MCF-7, and BT-474. Fuh states that the results obtained with the BT474 cells were very different from the results obtained with T47D and MCF-7 cells. Fuh, Abstract; page 13135, column 2, paragraphs 1-3; and bridging paragraph, pages 13135-13136. For example, Fuh states that both the G120R-hPRL analog and the G120R-hGH analog inhibited both MCF-7 cells and T47D cells. Fuh, page 13135, column 2, paragraph 3; and Figures 3C. In contrast, Fuh states that the results with BT-474 cells were very different. Fuh, bridging paragraph, pages 13135-13136; and Figure 3D.

Moreover, the data presented in Figure 3D show **minimal** inhibition of growth of BT-474 by **G120R-hGH, alone or together with $ZnSO_4$**. As noted in the legend to Figure 3D, the 100% value for all panels represents data from control cells treated with assay medium alone. The data for G120R-hGH + $ZnSO_4$ (filled circles) and the data for G120R-hGH without $ZnSO_4$ (open circles) show only about 10% growth inhibition at the concentrations tested.

Fuh notes that the growth-inhibitory effect of G120R-hPRL and G120R-hGH on BT-474 cells was "more pronounced" in the presence of added Zn^{2+}, but went on to state that "it is possible that the receptors on BT-474 cells are different from hPRL receptor..." Fuh, page 13136, column 1, lines 3-8.

Indeed, Fuh went on to study the BT-474 cell line a bit further, and found that, unlike MCF-7 cells, growth of BT-474 was **not** inhibited by PC4, an anti-hPRL receptor antibody. Fuh, page 13136, column 1, paragraphs 2-4; and Figures 4B and 4C.

Because the BT-474 cell line appears to behave differently from the T47D and MCF-7 cell lines, and because Fuh demonstrated **very little inhibition** of BT-474 cells with G120R-hGH (alone or together with $ZnSO_4$), no meaningful conclusion can be made from Fuh with respect to any effect of an hGH-based prolactin receptor antagonist and zinc on growth of an actual breast cancer cell. One skilled in the art would not have a reasonable expectation of success, based on the data presented in Figure 3D of Fuh with respect to G120R-hGH, alone or in combination with $ZnSO_4$.

The Office Action stated that Fuh "suggest increasing the affinity of G120R for the prolactin receptor to make it a more potent antagonist..." Office Action, page 7. However, first, it should be noted that Fuh does not disclose or suggest that zinc increases the affinity of an hGH-based antagonist for the prolactin receptor; nor does the '186 patent. Secondly, where Fuh does suggest increasing the affinity of the G20R-hGH for the prolactin receptor, Fuh does not mention the use of zinc to achieve such an increase. Instead, Fuh refers to papers describing hGH with variant amino acid sequences (Fuh, et al., 1992; Lowman et al, 1991; and Lowman and Wells, 1993), and suggests that "[s]uch a strategy could be applied here to improve either the hGH or hPL antagonists toward the hPRL receptor." Fuh, page 13137, column 1, lines 4-9. Thirdly, Fuh merely suggests that "perhaps the analogs may be more effective when used in conjunction with other growth inhibitors." Fuh, page 13137, column 1, lines 12-15.

It should be noted that Fuh does not mention testing any effect of $ZnSO_4$ on G120R-hGH-mediated growth inhibition of T47D cells or MCF-7 cells. However, the '186 patent clearly shows that $ZnSO_4$ had no significant effect on G120R-hGH-mediated growth inhibition of T47D cells.

For the reasons discussed above, the '186 patent **does not provide a reasonable expectation of success**, and indeed actually **teaches away** from a method as recited in instant claims 1-3 (and claims depending directly or indirectly therefrom) involving administering an hGH-based prolactin receptor antagonist and zinc. For the reasons discussed above, no meaningful conclusions can be reached from the data presented in Fuh with respect to the use of an hGH-based prolactin receptor antagonist and zinc, and Fuh does not provide a reasonable expectation of success with respect to the use of an hGH-based prolactin receptor antagonist and zinc in inhibition of breast cancer cell growth.

The '186 patent, alone or in combination with Fuh, would not suggest to a person of skill in the art a method as recited in any of claims 1-3, involving administering an hGH-based prolactin receptor antagonist and zinc, with a reasonable expectation of success. As such, the '186 patent, alone or in combination with Fuh, cannot render any of claims 1-5, 8, 9, 16, and 18 obvious.

Claim 17 over the '186 patent in view of Fuh and further in view of Aamodt

The Office Action stated that Fuh and the '186 patent do not teach administering zinc orally. The Office Action stated that Aamodt teaches that the administration of zinc orally is known. Applicants respectfully traverse the rejection.

As noted above: 1) the '186 patent **does not provide a reasonable expectation of success**, and indeed actually **teaches away** from a method as recited in instant claims 1-3 (and claims depending directly or indirectly therefrom) involving administering an hGH-based prolactin receptor antagonist and zinc; and 2) for the reasons discussed above, no meaningful conclusions can be reached from the data presented in Fuh with respect to the use of an hGH-based prolactin receptor antagonist and zinc, and Fuh does not provide a reasonable expectation of success with respect to the use of an hGH-based prolactin receptor antagonist and zinc in inhibition of breast cancer cell growth. As such, the '186 patent, alone or in combination with Fuh, cannot render any of claims 1-5, 8, 9, 16, and 18 obvious.

Aamodt does not cure the deficiencies of the '186 patent or Fuh. Aamodt relates to zinc metabolism in humans after oral and intravenous administration of Zn-69m. Aamodt neither discloses nor suggest a method involving administering an hGH-based prolactin receptor antagonist and zinc.

Claim 17 depends from claim 16, which in turn depends from claim 1, 2, or 3. The '186 patent, alone or in combination with Fuh, cannot render claim 17 obvious. Aamodt does not cure the deficiencies of the '186 patent or of Fuh. As such, the '186 patent, alone or in combination with Fuh and Aamodt, cannot render claim 17 obvious.

Claim 19 over the '186 patent in view of Fuh and further in view of Chen

The Office Action stated that the '186 patent and Fuh do not teach combining surgery with the method of treating breast cancer. The Office Action stated that Chen teaches that the primary therapy for women with breast cancer has been surgery. Applicants respectfully traverse the rejection.

As noted above: 1) the '186 patent **does not provide a reasonable expectation of success**, and indeed actually **teaches away** from a method as recited in instant claims 1-3 (and claims depending directly or indirectly therefrom) involving administering an hGH-based prolactin receptor antagonist and zinc; and 2) for the reasons discussed above, no meaningful conclusions can be reached from the data presented in Fuh with respect to the use of an hGH-based prolactin receptor antagonist and zinc, and Fuh does not provide a reasonable expectation of success with respect to the use of an hGH-based prolactin receptor antagonist and zinc in inhibition of breast cancer cell growth. As such, the '186 patent, alone or in combination with Fuh, cannot render any of claims 1-5, 8, 9, 16, and 18 obvious.

Chen does not cure the deficiencies of the '186 patent or Fuh. Chen was cited merely for stating that surgery has been a primary therapy for women with breast cancer. Chen neither discloses nor suggests a method

involving administering an hGH-based prolactin receptor antagonist and zinc.

Claim 19 depends from claim 4. The '186 patent, alone or in combination with Fuh, cannot render claim 17 obvious. Chen does not cure the deficiencies of the '186 patent or of Fuh. As such, the '186 patent, alone or in combination with Fuh and Chen, cannot render claim 19 obvious.

Conclusion as to the rejections under 35 U.S.C. §103(a)

Applicants submit that the above-discussed rejections under 35 U.S.C. §103(a) have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejections.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number TRCA-004.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: December 18, 2009

By: /Paula A. Borden, Reg. No. 42,344/
Paula A. Borden
Registration No. 42,344

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, CA 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

F:\DOCUMENT\TRCA\004\TRCA-004_Response_OA_11-24-09.doc